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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/403,440
Filing Date: January 19, 2000
Appellant(s): LANE, DAVID PHILIP

GINGER R. DREGER
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed July 1, 2009 appealing from the Office action mailed May 22, 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

A substantially correct copy of appealed claims 1, 2 and 8 appears on page 18 of the Appendix to the appellant's brief. The minor errors are as follows:

In claim 1

… "said p53-binding protein mdm2 is not, and comprising overexpressed"… on lines 2nd and 3rd is incorrect.

Claim 1 should read as follows:

Claim 1. An in vitro method for disrupting the binding of p53 and p53-binding protein mdm2 in a population of cancer cells in which said p53-binding protein mdm2 is not overexpressed, comprising administering to the cells a peptide, less than 25 amino acids in length, and comprising SEQ ID NO: 3.

(8) Evidence Relied Upon

Bottger et al. "Identification of novel mdm2 binding peptides by phage display" Oncogene, Vol. 13 (1996), pp.2141-2147.

McCann et al. "Amplification of the MDM2 gene in human breast cancer and its association with MDM2 and p53 protein status" British J Cancer, vol. 71 (1995), pp. 981-985.

Lee et al. "Apoptosis, cancer and the p53 tumor suppressor gene" Cancer and Metastasis Reviews, vol. 14 (1995), pp. 149-161.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject

matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bottger et al, 1996, Oncogene, 13: 2141-2147, in view of McCann A H et al, 1995, British J Cancer, 71(5): 981-5 and Lee JM et al, 1995, Cancer and metastasis Reviews, 14(2): 149-161.

Claims 1, 2 and 8 are as follows:

Claim 1. An in vitro method for disrupting the binding of p53 and p53-binding protein mdm2 in a population of cancer cells in which said p53-binding protein mdm2 is not overexpressed, comprising administering to the cells a peptide, less than 25 amino acids in length, and comprising SEQ ID NO: 3.

Claim 2. The method of claim 1 wherein the p53 is activated for DNA specific binding and transcription.

Claim 8. The method of claim 1 wherein the peptide has the property of competing with said p53-binding protein mdm2 for binding p53, but does not inhibit DNA specific binding property of p53.

It is noted that the claimed 19 amino acid peptide of SEQ ID NO:3 (PPLS**MPRFMDYWEGLN**ENG) or TIP 12/1 is derived from the wild type mdm2 binding site of p53 (the instant specification, p.24, paragraph before last and figure 1), in which the 12 amino acid peptide QETFSDLWKLLP is replaced with MPRFMDYWEGLN.

Bottger et al teach that the most potent peptide sequence **MPRFMDYWEGLN** (12/1 or IP3) containing the consensus sequence **P**XFXD**Y**W**XX**L and screened by phage display from the wild type mdm2 binding site of human p53 having the sequence PLSQETFSDLWKLLPENNV is superior than the wild type p53 peptide in **inhibiting the binding of the wild type 53 to mdm2** (table 1 on page 2142, figure 5 on page 2144, page 2144, first column, first paragraph). The 12 amino acid peptide MPRFMDYWEGLN (12/1 or IP3) taught by Bottger et al is the same as the 12 amino acid peptide MPRFMDYWEGLN within the 19 amino acid peptide of SEQ ID NO:3 of the instant application. Bottger et al teach that mdm2

is a **natural inhibitor of p53**, binding to p53 and inactivating p53 function as a transcriptional factor (abstract, p.2141, first column). Bottger et al further teach that the mdm2-p53 interaction is a much pursued target for the development of anti-cancer drug (abstract). Bottger et al further teach that the peptide represents a clear route towards the design of small synthetic molecules that will restore p53 function in human tumors (p.2141, second column, first paragraph, last three lines).

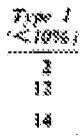
Although Bottger et al teach the peptide MPRFMDYWEGLN within SEQ ID NO:3, Bottger et al do not specifically teach SEQ ID NO:3, or a peptide of less than 25 amino acid in length and comprising SEQ ID NO:3. Further, although Bottger et al contemplates the use of the peptide MPRFMDYWEGLN to restore p53 function in cancers, Bottger et al do not teach a population of cancer cells in which mdm2 is not overexpressed. Bottger et al do not teach that: 1) p53 is activated for DNA specific binding and transcription, and 2) the peptide has the property of competing with mdm2 for binding p53, but does not inhibit DNA specific binding property of p53.

McCann et al teach that one of the objectives of the study is to determine the association of altered MDM2 with p53 staining in breast cancer patients (p.981, second column, last three lines of second paragraph, and especially Table III on page 983).

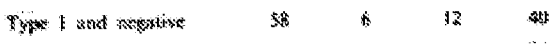
Table III Association of MDM2 protein status with nuclear p53 staining

p53 nuclear accumulation[a]	Total no. of cases	MDM2 nuclear expression[b] Type 2 (10–30%)	Type 1 (<10%)	Negative
Type 2 and 3	37	1	2	34
Type 1 and negative	58	6	12	40
Total	95	7	14	74

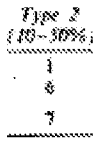
From table III, there are total **14** patients that have **less than 10%** of tumor cells positive for MDM2 (type 1 MDM2), as shown in the column below taken from table III:



From said total 14 patients, **12** of them have **low level of p53**, i.e. having less than 10% of tumor cells stained with p53 (p53, type 1 and negative column taken from table III as shown below, and p.982, second column, last five lines of first paragraph). Low level of p53 staining is described by McCann as having 0-10% cells positive for p53 staining (abstract, lines 8-9).



From table III, there are also total 7 patients that have 10-50% cells positive for MDM2 (type 2 MDM2), 6 of them have low level of p53, with less than 10% of tumor cells stained with p53 (p53, type 1 and negative, as shown in the above column, and the column shown below taken from Table III, and in addition, abstract and p.983, first column, paragraph under Expression).



From table III, one would reasonably conclude that **low level of p53 is prevalent** in most breast cancer patients that express mdm2, having either **less than 10%** of cancer cells positive for MDM2 (type 1 MDM2) (14 patients) or **10-50%** cancer cells positive for MDM2 (type 2 MDM2) (7 patients). Further, there are twice as many patients having less than 10% of tumor cells positive for MDM2 (type 1 MDM2) (total 14 patients from 95 cases, or 15%) as compared

to patients having 10-50% cells positive for MDM2 (type 2 MDM2) (total 7 patients from 95 cases, or 7%).

It is reasonable to interpret that those 14 patients that have **less than 10% of tumor cells** positive for MDM2 (type 1 MDM2) have low level of MDM2 staining, or MDM2 that is **not overexpressed**, in view that there is no clear definition of "cells that do not overexpress mdm2" in the specification and the claims, and in view that McCann et al describe low levels of p53 staining as having 0-10% cells positive for p53 (McCann et al, abstract, lines 8-9). The specification discloses that cells that do not overexpress mdm2 includes all cells in which mdm2 is present at low or normal level (p.6, lines 25-32). It is not clear, however, in the claims and from the disclosure in the specification "mdm2 is not overexpressed" is as compared to what. Further, it is not clear what constitutes low or normal levels and what levels of mdm2 are considered low or normal level. Although the specification discloses an example of sarcoma cells disclosed in WO 93/20238 as cells that overexpress mdm2, the specification does not have an example of low or normal level of mdm2.

McCann et al further teach that amplification of mdm2 gene is not frequent in breast cancer (abstract, p.981, second column, first paragraph) and that prior studies show that in familial breast cancer patients, **mutations of p53 are not detected** (p.984, first column, first three lines). Further, McCann et al conclude in the abstract that **alteration** in MDM2 and p53 may represent alternative pathways in tumorigenesis, but they are **not mutually exclusive in all cases** (abstract, last two lines), i.e. mutation of p53 could be found in cancers that also have mutation of mdm2. Specifically, McCann teach that 1/3 of **amplified MDM2 breast cancer** tumors also have **increased level of p53** staining (10-50% of tumor nucleic positive or type 2

p53 staining) (p.984, first column, last paragraph, asbtract). Such an increase in p53 in breast cancer would be likely due to mutation of p53, when based on previous study of Singh et al, 1993, showing that accumulation of p53 is synonymous with the presence of p53 mutations (McCann et al, p.984, first column, last paragraph, bridging second column). McCann et al teach that this is similar to a previous study of gliomas (Reifenberger et al, 1993), in which amplified MDM2 samples also display increased level of p53 (p.984, first column, first three lines). McCann et al teach that, however, previous studies of **sarcoma** (Oliner et al, 1992, and Leach et al, 1993a) report that these p53 mutations have not found in any MDM2 amplified samples, suggesting that MDM2 amplification and p53 exonic mutations may be mutually exclusive (p.984, first column, last paragraph, bridging second column). Thus, it is reasonable to interpret from the teaching of McCann et al, that different from previously reported sarcoma, in breast cancer, MDM2 amplification and p53 mutation are **not mutually exclusive**. That is, breast tumors without MDM2 amplification do not necessarily have p53 mutation, **suggesting that low level of p53 is more likely due to the binding of and inhibition by mdm2 in breast cancer**, rather than by mutation of p53**.**

Lee et al teach that p53 functions as a transcriptional factor, via its binding to specific DNA (p. 150). Lee et al teach that p53 could induce apoptosis and cell cycle arrest, and that loss of p53 function causes increased resistance to chemotherapeutic agents (abstract).

It would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made to add to the potent inhibitor peptide MPRFMDYWEGLN (12/1 or IP3) taught by Bottger et al flanking wild type p53 amino acids, such as those p53 amino acids from

the wild type mdm2 binding site of p53 sequence PLSQETFSDLWKLLPENNV taught by Bottger et al, to increase the stability of the peptide, via increasing the size of the peptide.

It would have been obvious to use the potent inhibitor peptide taught by Bottger et al with flanking wild type p53 amino acids to displace the binding of mdm2 from p53 for restoring p53 function in cancer cells in which low level of p53 is likely due to inhibition by mdm2, in view of Bottger et al, because: 1) mdm2 is a natural inhibitor of p53, by binding to p53 and inactivating p53 function as taught by Bottger et al, 2) loss of p53 function in cancer cells is correlated with increased resistance to chemotherapeutic agent, as taught by Lee et al.

Further, it would have been obvious to use breast cancer cells that express mdm2 taught by McCann et al, including those cells from breast cancer patients that have less than 10% mdm2 positive cancer cells taught by McCann et al, and interpreted by the Examiner as not overexpressing mdm2, as target for the amino acid sequence comprising the peptide taught by Bottger et al, to restore the function of p53, because of the following reasons:

1) p53 level is low (0-10% cells positive for p53) in most breast cancer patients that express mdm2, as taught by McCann et al, including those cells from breast cancer patients that have less than 10% mdm2 positive cancer cells taught by McCann et al, and interpreted by the Examiner as not overexpressing mdm2,

2) mdm2 is a natural inhibitor of p53, via binding of mdm2 to p53 as taught by Bottger et al, and

3) mutation of p53 is not detected in familial breast cancer patients, as taught by McCann et al. Further, MDM2 amplification and p53 mutation are not always mutually exclusive in all cancers, as taught by McCann et al. That is, breast cancers without MDM2 amplification do not

necessarily have p53 mutation, suggesting that in breast cancers, **low level of p53 is likely due to the binding of and inhibition of p53 by mdm2, rather than by p53 mutation**.

One would have a reasonable expectation of success in displacing the binding of p53 and mdm2 by the inhibitor peptide taught by Bottger et al with flanking wild type p53 amino acids in breast cancer cells that have less than 10% staining of mdm2, i.e., that do not overexpress mdm2, because the peptide taught by Bottger et al contains a consensus sequence, that is a potent inhibitor of mdm2 and p53 interaction, as taught by Bottger et al, and because in breast cancer, low level of p53 is likely due to the binding of and inhibition of p53 by mdm2, rather than by p53 mutation, in view of the teaching of McCann et al.

One would have been expected that the peptide taught by the combined art does not inhibit the DNA specific binding property of p53, because the peptide taught by the combined art would disrupt the binding of p53 to mdm2 by targeting at the specific p53 binding site for mdm2, as taught by Bottger et al, which is different from the DNA binding site of p53. One would have expected that that p53 is activated for DNA specific binding and transcription, because the activity of p53 is to function as a transcriptional factor, via its binding to specific DNA, as taught by Lee et al.

(10) Response to Argument

The response asserts as a summary as follows:

The documents cited in support of the rejection under 35 U.S.C.103 do not properly represent the state of the art at the priority date of this application, and the rejection itself is based on improper hindsight reconstruction of the claimed invention. Furthermore, the Examiner

misrepresented the teaching of the secondary reference, McCann AH et al., 1995 (British J Cancer, 71 (5):981-5), and failed to give proper weight and consideration to two expert Declarations under 37 C.F.R. §1.132 by Professor Karen Vousden.

The response has been considered but is not found to be persuasive for the following reasons:

The claimed invention is obvious over the cited art for reasons set forth above. The cited references, including McCann et al reference, are reasonably interpreted and represent the art at the time the invention was made. Further, none of the references cited in the response teach that amplification of mdm2 and mutation of p53 in **breast cancers** are mutually exclusive or vice versa, and dispute the teaching of the references cited by the Examiner.

Moreover, the rejection is not based on hindsight reconstruction. One would have been motivated to use a peptide comprising the inhibitor peptide taught by Bottger et al to disrupt the interaction between p53 and mdm2 for restoring the function of p53 in cancer cells, as suggested by Bottger et al, because mdm2 is a natural inhibitor of p53 function when binding to p53, as taught by Bottger et al. One would have been motivated to use as cancer cells, breast cancer cells that express mdm2, including those cells from breast cancer patients that have less than 10% mdm2 positive cancer cells taught by McCann et al, which is interpreted by the Examiner as not overexpressing mdm2, because:

1) low level of p53 is found in most breast cancer cells that express mdm2, including those cells from breast cancer patients that have less than 10% mdm2 positive cancer cells, as taught by McCann et al, and

2) low level of p53 in breast cancer is likely due to the binding of and inhibition of p53 by mdm2, rather than by mutation of p53, in view of the teaching of McCann et al.

Moreover, the two Declarations by Professor Karen Vousden have been carefully considered, but are not found to be persuasive for withdrawing the rejection.

The response recites legal standard on pages 8-9.

The response further asserts as follows:

a) Appellant does not contest the Examiner's reading of Bottger et al and Lee et al but submit that the Examiner has mischaracterized the teaching of McCann et al.

Appellant submits that the Examiner has misunderstood and mischaracterized the teaching of McCann et al. In particular, the Examiner is wrong to say that McCann et al teach that in cancers which do not overexpress mdm2 the protein expression of mdm2 is significantly associated with low levels of p53. To the contrary, the teaching of McCann et al is that in those samples which show overexpression of mdm2, p53 is reduced.

As defined in the present application, "cells that do not overexpress mdm2" include all cells in which mdm2 is present at low or normal levels, which can be assessed, e.g., by immunological measurement of mdm2 concentration (page 6, lines 25-32).

A protein can be overexpressed in a cell for a number of reasons. One possible reason is that the gene expressing the protein is amplified. However, overexpression can also take place in the absence of gene amplification, e.g., due to an alteration in the normal regulation of the rate of synthesis of the protein and/or in the rate of destruction of the protein. Gene amplification is only one of a number of different mechanisms by which overexpression of a protein may occur.

McCann et at discloses studies into the frequency of Mdm2 overexpression in breast cancers. They look at both gene amplification and protein expression and find that only 7% of these cancers show overexpressed Mdm2.

Indeed, McCann et al expressly states that: "Interestingly, at the mRNA level, two studies found increased MDM2 expression with no apparent alteration in MDM2 copy number (Buesco-Ramos et al, 1993, Sheikh et al, 1993), suggesting that mechanisms other than gene amplification may play a role in deregulating the expression of MDM2" (page 981, right column, first paragraph).

In McCann et al, overexpression at the protein level was assessed by immunological measurement. 7% of the samples were found to show 10-50% mdm2 nuclear staining, and these samples were designated as MDM2+ cells. This is in spite the fact that only that 4% of tumor samples assayed have altered mdm2 copy number - as noted above, overexpression of a protein can occur even without gene amplification.

McCann et al report that MDM2+ status was significantly associated with low levels of p53 (page 983, left column, last paragraph). As explained above, MDM2+ status indicates overexpression of mdm2. Thus, as noted above, contrary to the Examiner's reading, McCann et al teach that p53 levels are reduced in those samples which show overexpression of mdm2.

The response has been considered but is not found to be persuasive for the following reasons:

Contrary to the response assertion, the data in Table III (p.983) from McCann et al show that p53 levels are low (i.e., less than 10% cancer cells positive for p53) in **most** breast cancer

patients that express mdm2, including those 14 patients or 15% patients having less than 10% cancer cells positive for mdm2, interpreted by the Examiner as not overexpressing mdm2, and **not just in those 7% mdm2+ patients** that have 10-50% cancer cells positive for mdm2, interpreted by the response as overexpressing mdm2.

The following is detailed explanation of the data in table III of McCann et al.

McCann et al teach that one of the objectives of the study is to determine the association of altered MDM2 at the DNA and protein levels with p53 staining in breast cancer patients (p.981, second column, last three lines of second paragraph, and especially Table III on page 983).

Table III Association of MDM2 protein status with nuclear p53 staining

p53 nuclear accumulation[a]	Total no. of cases	MDM2 nuclear expression[b] Type 2 (10–90%)	Type 1 (<10%)	Negative
Type 2 and 3	37	1	2	34
Type 1 and negative	58	6	12	40
Total	95	7	14	74

From table III, there are total 14 patients that have **less than 10%** of tumor cells positive for MDM2 (type 1 MDM2), as shown in the column below taken from table III:

Type 1 (<10%)
2
12
14

From said total 14 patients, 12 of them have **low level of p53**, i.e. having less than 10% of tumor cells stained with p53 (p53, type 1 and negative taken from table III as shown below,

and p.982, second column, last five lines of first paragraph). Low level of p53 staining is described by McCann as having 0-10% cells positive for p53 staining (abstract, lines 8-9).

Type 1 and negative	58	6	13	80

From the total 7 patients that have 10-50% cells positive for MDM2 (type 2 MDM2), 6 of them have low level of p53, with less than 10% of tumor cells stained with p53 (p53, type 1 and negative in the column above, and the column shown below taken from Table III, and in addition, abstract and p.983, first column, paragraph under Expression).

Type 2 (10–50%)
1
6
7

Thus, low level of p53 is **prevalent in most** breast cancer patients that express mdm2, having either **less than 10%** of tumor cells positive for MDM2 (type 1 MDM2), interpreted by the Examiner as not overexpressing mdm2, or **10-50% cells** positive for MDM2 (type 2 MDM2), interpreted by the response as overexpressing mdm2. Further, there are **twice** as many patients having less than 10% of tumor cells positive for MDM2 (type 1 MDM2) (total 14 patients from 95 cases, or 15%) as compared to patients having 10-50% cells positive for MDM2 (type 2 MDM2) (total 7 patients from 95 cases, or 7%).

The response further asserts as follows on pages 11-13:

b). The scope and content of the prior art and the differences between the claimed invention and the prior art when making the rejection

(1) *Level of skill in the art*

The invention is from the field of molecular biology. In this field, the level of ordinary skill has been determined to be high, usually represented by a scientist with a PhD in the relevant field.

(2) *Scope and content of the prior art*

Contrary to the Examiner's assertions, the state of the art in the relevant time frame, when taken as a whole, indicated that inhibition of the mdm2/p53 interaction in tumors in which mdm2 is expressed at normal levels (i. e., is not overexpressed) could be non-specifically toxic and consequently would not be a good approach for tumors without Mdm2 overexpression.

The first Vousden Declaration

The present application claims priority from UK application GB9708092.3 filed on April 22, 1997. In Paragraphs 6 through 9 of the first Vousden Declaration, Professor Vousden explains that around that time (and around the 1996 publication date of the McCann paper), it was understood that inhibition of p53 function is important for the development of many cancers. It was also understood that this might be the consequence of a number of different events, including, but not limited to,

1. mutation within the p53 gene;

2. overexpression of Mdm2 - a known negative regulator of p53; and

3. expression of the human papilloma virus E6 protein,

and that these alterations are mostly mutually exclusive. In particular, in Paragraph 7 of the first Vousden Declaration Professor Vousden cites Crook et al, Oncogene 6:873-875 (1991); Scheflher et al., PNAS 88:5523-5527, 1991; Crook et al., Lancet 339:1070-1073, 1992; Leach et al., Cancer Res 53:2231-2234, 1993; and Oliner et al., Nature 358:80-83, 1992 (all of record) as

representative of the general knowledge in the art at the relevant time frame that tumors with E6 or Mdm2 overexpression do not have mutated p53 and via versa, and that it is only necessary to inactivate p53 through one mechanism.

Professor Vousden cites US 09/403,440 to show that it was also known at the priority date of the present application that: (i) p53 binds Mdm2; (ii) Mdm2 inhibits p53 activity; (iii) inhibition of Mdm2 in normal cells will activate p53; and (iv) Mdm2 is overexpressed in some tumors and this is often associated with retention of wild-type p53. (First Vousden Declaration, Paragraph 8).

Papers published in 1995 (Jones et al., Nature 378:206-208, 1995; Montes de Oca Luna et al., Nature 378:203-206, 1995 - of record) disclosed experimental results showing that deletion of Mdm2 in mice causes embryonic lethality owing to the activation of p53. These findings indicated to those of ordinary skill in the art that while inhibition of Mdm2 can cause activation of p53 in cells where Mdm2 is not overexpressed, this activation is very deleterious to normal tissue. As stated in Paragraph 9 of her first Declaration, these findings suggested to Professor Vousden

"that a therapy to inhibit mdm2/p53 would not be selective for tumours where Mdm2 is expressed at normal levels. Instead, the findings suggested that such a therapy could well be non-specifically toxic and consequently would not be a good approach for tumours without Mdm2 over-expression. "

The response has been considered but is not found to be persuasive for the following reasons:

(1) Level of skill in the art

The level of skill in the art is high.

(2) Scope and content of the prior art and the first Vousden Declaration

The Declaration and the submitted references have been carefully considered, but are not found to be persuasive.

A review of Leach et al and Oliner et al show that MDM2 amplification and p53 mutation are mutually exclusive, in **sarcoma**. Crook et al, 1991, and 1992, and Scheffner et al teach relationship between p53 mutation and human papillomavirus (HPV) cervical cancers.

McCann et al, however, conclude in the abstract that alteration in MDM2 and p53 may represent alternative pathways in tumorigenesis, but they are **not mutually exclusive in all cases** (abstract, last two lines). Thus, contrary to the response assertion, in view of the teaching of McCann et al, and Reifenberger et al, as referred by McCann et al, at the time the invention was made, one would have reasonably concluded that different from previously reported sarcoma or HPV cervical cancer, in breast cancers and gliomas, mdm2 amplification and p53 mutation are **not mutually exclusive.** That is, breast cancers that do not have amplified mdm2 do not necessarily have p53 mutation, indicating that low level of p53 in breast cancer is more likely due to the binding of and inhibition by mdm2, rather than by mutation of p53. This is further supported by the fact that previous studies have shown that familial breast cancer patients do not have p53 mutations, as taught by McCann et al (p.984, first column, first paragraph).

Concerning **non-specific toxicity to normal cells**, it is noted that the claimed method is drawn to ***in vitro*** method for testing the disruption of the binding of p53 to mdm2, and thus the issue of toxicity to normal cells is not germane here. Further, even if the issue of non-specific toxicity to normal cells were considered, at the time the invention was made, it is routine to

specifically target cancer cells, such as using a ligand specific for the tumors to deliver a therapeutic agent, or by direct administration of the therapeutic agent to cancers. Such targeting would reduce or limit the exposure of normal cells to the non-specific toxicity of the therapeutic agent.

The response further asserts as follows on pages 13-16:

(3) *Differences between the claimed subject matter and the prior art and the second Vousden Declaration*

Proper obviousness analysis requires that the Examiner occupy the mind of one skilled in the art, who has no knowledge of the claimed invention, is aware of and understands the totality of pertinent knowledge at the time the claimed invention was made, and who is normally guided by the then-accepted wisdom in the art. Appellant submits that an analysis properly conducted respecting these principles must necessarily lead to the conclusion that inhibition of the mdm2/p53 interaction in cancers that do not overexpress mdm2 would not be an effective approach for activating the tumor suppressor function of p53.

In view of the fact that, as discussed above, at the priority date of the present application there were several mechanisms suggested for the inhibition of p53 function, it was assumed that in tumors that do not overexpress Mdm2, p53 is inhibited by a different mechanism. See, first Voussen Declaration, Paragraph 11.

The results of McCann et al show that only 7% of the tested breast cancers overexpress Mdm2. Since, as discussed above, at the time of the McCann et al. paper was published in was generally held that inhibition of the p53/Mdm2 interaction would only be effective in cancers

that overexpress Mdm2, the real teaching of the McCann et al. paper is that inhibition of the p53/Mdm2 would be an effective treatment approach only in the case of a small proportion of breast cancers, i.e. breast cancers that overexpress Mdm2. As stated in Paragraph 15 of the first Vousden Declaration:

> The Examiner is incorrect in her view that McCann et al. teach that in cancers which **do not express** (emphasis added) mdm2, such as breast cancer cells, the protein expression of mdm2 is significantly associated with low levels of p53. The study by McCann et al shows that although most breast cancers do not over-express Mdm2, a few of them show elevated Mdm2 expression, and these tumours are significantly associated with low (i.e., wild type) p53 levels. McCann et al. state that "at the protein level, MDM2 + tumours were significantly associated with tumours having low levels of p53 staining. " (Summary, lines 7/8) This means that those few breast cancers that over-express Mdm2 tend to show low levels of p53 - indicating a retention of wild type p53.

The response has been considered but is not found to be persuasive for the following reasons:

Contrary to the response assertion, in view of the teaching of McCann et al, and Reifenberger et al, as referred by McCann et al, at the time the invention was made, one would have reasonably concluded that different from previously reported sarcoma or HPV cervical cancer, mdm2 amplification and p53 mutation do not always have to be mutually exclusive, such as in breast cancers, or in gliomas, supra. That is, breast tumors without MDM2 amplification do not necessarily have p53 mutation, indicating that in breast cancer, low level of p53 is more likely due to the binding of and inhibition of p53 by mdm2. This is further supported by the fact

that previous studies have shown that familial breast cancer patients do not have p53 mutations, as taught by McCann et al (p.984, first column, first paragraph).

Moreover, the response misinterpretes the teaching of McCann et al. McCann et al **do not teach** that inhibition of the p53/Mdm2 would be an effective treatment approach **only** in the case of a small proportion of breast cancers, i.e. breast cancers that overexpress mdm2. Nowhere in McCann et al that one find such a claimed teaching that inhibition of the p53/mdm2 would be an effective treatment approach **only** in the case of a small proportion of breast cancers, i.e. breast cancers that overexpress Mdm2. Contrary to the response assertion, in view that:

1) low level of p53 in breast cancer is more likely due to inhibition by mdm2, rather than by p53 mutation, in view of the teaching of McCann et al, and Bottger et al, supra, and

2) p53 level is breast cancer is low in most breast cancer, as taught by McCann et al, supra, including in 15% of tested breast cancer patients having less than 10% cancer cells positive for mdm2, which is interpreted as not overexpressing mdm2,

one would have a reasonable expectation that p53 function would be restored in breast cancer cells, including cancer cells from 15% of tested breast cancer patients having less than 10% cancer cells positive for mdm2, when using a polypeptide comprising the peptide taught by Bottger et al, which peptide taught by Bottger et al is a potent inhibitor of mdm2 and p53 interaction.

Concerning the first two lines of Paragraph 15 of the first Vousden Declaration, it is noted that the issue does not concern cancers which **do not express** mdm2, as stated in the Declaration, because without expression of mdm2, the issue of disrupting binding of p53 to mdm2 is moot.

The response further asserts as follows:

The second Vousden Declaration

In addressing the Examiner's finding that her first Declaration was not persuasive, in her second Declaration Professor Vousden provides a more detailed explanation of the teaching of McCann et al. As explained in Paragraph 4:

> McCann et al. show that 7/97 tumours have high levels of MDM2 expression (type 2, 10-50% staining) and that these are associated with low levels of p53. Table II of McCann et al. only shows results for tumours that are either amplified for the MDM2 gene (samples 10, 16 and 19 - of which only 2 show type 2 MDM2 staining) or tumours that show high MDM2 protein expression (7. e., 10-50% staining) without amplification of the gene (tumours 15, 30, 45, 47 and 60). The authors define these 7 as the MDM2 + tumours and state that these show a significant association with low levels of p53. So tumours with high MDM2 (as defined by type 2 staining) are likely to have low p53 - this is what the authors conclude from their study.

Professor Vousden goes on explaining that, since on page 983 the authors define MDM2+ as "[10-50% of tumor nuclei positive (MDM2+) Table 1]" and "MDM2+" (type 2 staining)," it is absolutely clear that by "MDM2+ tumors" the authors intended to refer to those 7 tumors with high MDM2 expression. Second Vousden Declaration, Paragraph 7. Thus, the Examiner incorrectly interpreted the authors' statement that "MDM2 tumors were significantly associated with tumors having low levels of p53 staining" to mean that "not only those few cancers that over-express Mdm2 tend to show low levels of p53, but those that do not over-

express mdm2 also show low levels of p53." (Office Action mailed on September 11, 2007, page 5).

While Professor Vousden recognizes that based on the data shown in Table III of the McCann et al. paper, it may be possible to conclude that even the tumours that express lower amounts of MDM2 (type 1 tumours, less than 100% staining) are associated with p53, she notes that the "authors of McCann et al do not pay much regard to this as they limit their comments to the 7 MDM2 + tumours and one might be reluctant to draw conclusions from data that the authors have chosen not to highlight themselves." Second Vousden Declaration, Paragraph 9.

Furthermore, even if one came to such conclusion, the data would still not tell that tumors that do not overexpress MDM2 are also associated with p53, as the Examiner has concluded. As Professor Vousden explains in Paragraph 10 of her second Declaration: The problem here is that we don't know what normal expression is - and it is quite possible that the type 1 expression is [sic] also represents over-expression of MDM2 compared to normal (there is no normal tissue in the McCann et al. study for comparison). The fact that most of the tumours are apparently negative for MDM2 staining (74/95) does not mean that they don't express any MDM2 - only that it is below the level of detection in this assay. For this reason it is quite hard to interpret the meaning of the less than 10% expression, which is probably why the authors have chosen to base their conclusion on the tumors that clearly over-express MDM2 - that is the type 2 staining ones.

The response has been considered but is not found to be persuasive for the following reasons:

From table III in McCann et al (McCann et al, p.983, supra), it is clear that low level of p53 is **prevalent in most** breast cancer patients that express mdm2, having either **less than 10%**

of tumor cells positive for MDM2 (type 1 MDM2), which is interpreted by the Examiner as not overexpressing mdm2, supra, or **10-50% cells** positive for MDM2 (type 2 MDM2), which is interpreted by the response as overexpressing mdm2, supra. Further, there are **twice** as many patients having less than 10% of tumor cells positive for MDM2 (type 1 MDM2) (total 14 patients from 95 cases, or 15%) as compared to patients having 10-50% cells positive for MDM2 (type 2 MDM2) (total 7 patients from 95 cases, or 7%), supra. Moreover, although McCann et al do not specifically discuss in the text the 15% of tested breast cancers patients that have less than 10% of cancer cells that are positive for mdm2, and also have low level of p53, the fact that their data are included in Table III (McCann et al, p. 983, supra) for studying association between alteration of mdm2 and the level of p53 show their validity as well.

Concerning paragraph 10 of the second Declaration, the limitation "not overexpressed as compared to **normal"** is not recited in the claims or defined in the specification, and thus the issue of whether no normal tissue is recited in McCann et al is not germane here.

Moreover, the response interpretation that less than 10% cells positive for mdm2 could also represent over-expression of mdm2 would **not be consistent** with the definition of McCann et al for those patients with less that 10% cells positive for p53 as having low level of p53 (abstract, lines 8-9). It is noted that the specification discloses that not overexpressing mdm2 include all cells in which mdm2 is present at low or normal levels (p.6, lines 25-32).

Concerning those breast cancer patients that are negative for mdm2 staining, as recited in paragraph 10 of the second Declaration, whether they are below the level of detection in the assay taught by McCann et al, but could be detected in other assays, is not germane here, because

when based on McCann et al, for those patients without expression of mdm2, the issue of disrupting binding of p53 to mdm2 is moot.

In conclusion, the claimed invention is obvious over Bottger et al, in view of McCann et al and Lee et al, for reasons set forth above and in previous Office actions.

The response further asserts as follows:

c. The combined teaching of Bottgger et al., McCann et al and Lee et al. is that targeting of the mdm2/p53 interaction is for use specifically in cells where mdm2 is overexpressed.

Bottger et al. teaches that the interaction between mdm2 and p53 may be a useful target in cells where mdm2 is overexpressed:

> "In several different tumour systems, including human sarcomas, the mdm2 protein (or its human homolog hdm2) is overexpressed but the p53 gene remains wild type (Oliner et al, 1992). This suggests that in these tumours the normal tumour suppressor function of p53 is being inactivated by the presence of abnormally high levels of mdm2. In theory, such tumours should be susceptible to therapeutic moieties that disrupt the mdm2/p53 interaction, restoring wild type p53 function." (Page 2141, right column, first paragraph, emphasis added).

Accordingly, one of ordinary skill in the art reading Bottger et al. would believe that therapeutic targeting of the mdm2/p53 interaction is of use specifically in cells where mdm2 is overexpressed.

As discussed above, there is nothing in McCann et al, when read and understood correctly, to contradict the teaching of Bottger et al or to suggest that targeting of the mdm2/p53 interaction may also be of use when mdm2 is not overexpressed.

This is clearly supported by the conclusion of the first Vousden Declaration that based on the combined teaching of the cited references one of skilled in the art would conclude that "a therapy based on the 12 amino acid peptide would only be expected to be effective in 7% of breast cancers (i. e., those with over-expressed Mdm2) and would suggest that most breast cancers would not benefit from such therapy." First Vousden Declaration, Paragraph 16.

Lee et al. has been relied on for allegedly teaching that p53 could induce apoptosis and cell cycle arrest, and that loss of-53 function causes increased resistance to chemotherapeutic agents. This teaching does modify the combined teaching of Bottger et al. and McCann et al. that targeting of the mdm2/p53 interaction is of use specifically in cells where mdm2 is overexpressed.

The response has been considered but is not found to be persuasive for the following reasons:

Although as an example, Bottger et al teach that in tumors, such as sarcomas, where the mdm2 is overexpressed and represses p53, and low level of p53 is not due to mutated p53, such tumors should be susceptible to disruption of the interaction of mdm2 and p53, nowhere that one find in Bottger et al the teaching that disruption of the interaction of mdm2 and p53 is or should be limited only those cancers that overexpress mdm2. Bottger et al teach that mdm2-p53 interaction is a much persued target for the development of anti-cancer drugs, in view that mdm2 binds to p53 and inactivates p53 function (abstract, first 7 lines). One would reasonably interpret

from the teaching of Bottger et al that targeting mdm2-p53 interaction should be persued in **any** cancers where low level or function of p53 is likely due to the binding of and consequently, suppression of p53 by mdm2.

One would have been motivated to use a peptide comprising the inhibitor peptide taught by Bottger et al to disrupt the interaction between p53 and mdm2 for restoring the function of p53 in cancer cells, as suggested by Bottger et al, including breast cancers that have less than 10% cancer cells positive for mdm2, taught by McCann et al, because:

1) mdm2 is a natural inhibitor of p53 function when binding to p53, as taught by Bottger et al, and

2) p53 level is breast cancer is low in most breast cancer, as taught in Table III of McCann et al, supra, including in 15% of tested breast cancer patients having less than 10% cancer cells positive for mdm2, which is interpreted by the Examiner as not overexpressing mdm2, and

3) in breast cancer, low level of p53 is more likely due to the binding of and inhibition by mdm2, rather than by mutation of p53, in view of the teaching of McCann et al, and Bottger et al, supra.

Further, there is nothing in the art suggesting that the 12 amino acid peptide would be only effective in those 7% of breast cancer patients that have 10-50% cells positive for mdm2, which is interpreted by the response as overexpressing mdm2. Contrary to the response assertion, one would have a reasonable expectation of success in displacing the binding of p53 and mdm2 by the inhibitor peptide taught by Bottger et al with flanking wild type p53 amino

acids in the population of breast cancer cells that have less than 10% staining of mdm2, interpreted as not overexpressing mdm2, because the peptide taught by Bottger et al contains a consensus sequence, that is a potent inhibitor of mdm2 and p53 interaction, as taught by Bottger et al, and because:

1) p53 level is breast cancer is low in most breast cancer, as taught in Table III of McCann et al, supra, including in 15% of tested breast cancer patients having less than 10% cancer cells positive for mdm2, which is interpreted as not overexpressing mdm2, and

2) low level of p53 in breast cancer is not expected to be due to mutation of p53, in view of the teaching of McCann et al, and thus, low level of p53 is more likely due to the binding of and suppression by mdm2, in view that mdm2 is a natural inhibitor of p53, as taught by Bottger et al.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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Patent Examiner

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